Romiplostim for temozolomide-induced thrombocytopenia in glioblastoma: The PLATUM trial

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Abstract: OBJECTIVE To determine the efficacy of the thrombopoietin receptor agonist romiplostim for the prevention of temozolomide-induced thrombocytopenia in newly diagnosed glioblastoma. METHODS In the PLATUM phase II open-label, multicenter, single-arm trial, patients diagnosed with Common Terminology Criteria for Adverse Events grade 3 or 4 thrombocytopenia during chemoradiotherapy received weekly subcutaneous romiplostim injections. PLATUM aimed at demonstrating that the percentage of thrombocytopenic patients treated with romiplostim able to complete 6 cycles of maintenance temozolomide chemotherapy exceeded 10% (0 = 0.10; A = 0.35). Using type I error equal to 0.05% and 95% power, 31 patients had to be recruited. According to a Fleming 2-step design with a preplanned interim analysis after recruitment of 20 patients (step 1), the trial was terminated early for success. RESULTS Twenty patients were enrolled in step 1. Median age was 61 years (range 33-73). Twelve patients received 6 temozolomide cycles, corresponding to a success rate of 60% (95% confidence interval 36%-81%). Four patients discontinued temozolomide because they did not respond to romiplostim, 2 for progression, and 2 for adverse events unrelated to romiplostim. CONCLUSION The thrombopoietin receptor agonist romiplostim improves exposure to chemotherapy in patients with glioblastoma experiencing temozolomide-induced thrombocytopenia. CLINICALTRIALSGOV IDENTIFIER NCT02227576. CLASSIFICATION OF EVIDENCE This study provides Class IV evidence that for patients with glioblastoma and thrombocytopenia, romiplostim is effective for the secondary prophylaxis of temozolomide-induced thrombocytopenia.

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Romiplostim for temozolomide-induced thrombocytopenia in glioblastoma: the PLATUM trial

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Statistical analysis

The statistical analysis was performed by P. Devos at Lille University and Lille University Hospital, France, in an academic setting.

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Emilie Le Rhun has received research grants from Mundipharma and Amgen and honoraria for lectures or advisory board from Abbvie, Daiichy Sankyo, Mundipharma and Novartis.

Olivier Chinot has received research grant from Roche, and honoraria for lectures or advisory board from Celldex, Abbvie, Servier.

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All remaining authors (Patrick Devos, Caroline Houillier, Stéphanie Cartalat, Anna Luisa Di Stefano, Clément Lepage, Nicolas Reyns and François Dubois) report no disclosures.

Abstract

Objective: To determine the efficacy of the thrombopoetin receptor agonist, romiplostim, for the prevention of temozolomide-induced thrombocytopenia in newly diagnosed glioblastoma.

Methods: In the PLATUM phase II open-label, multicenter single arm trial, patients diagnosed with CTCAE grade 3 or 4 thrombocytopenia during chemoradiotherapy received weekly subcutaneous romiplostim injections. PLATUM aimed at demonstrating that the percentage of thrombocytopenic patients treated with romiplostim able to complete 6 cycles of maintenance temozolomide chemotherapy exceeded 10% (p0=0.10; pA=0.35). Using type I error equal to 0.05 and 95% power, 31 patients had to be recruited. According to a Fleming's two step design with a preplanned interim analysis after recruitment of 20 patients (step 1), the trial was terminated early for success.

Results: Twenty patients were enrolled in step 1. Median age was 61 years (range: 33-73). Twelve patients received six temozolomide cycles, corresponding to a success rate of 60% (95% confidence interval 36-81%). Four patients discontinued temozolomide because they did not respond to romiplostim, two for progression, and two for adverse events unrelated to romiplostim.

Conclusion: The thrombopoetin receptor agonist romiplostim improves exposure to chemotherapy in glioblastoma patients experiencing temozolomide-induced thrombocytopenia.

Clinicaltrials.gov identifier: NCT02227576

Classification of Evidence: This study provides class IV evidence that for patients with glioblastoma and thrombocytopenia, romiplostim is effective for the secondary prophylaxis of temozolomide-induced thrombocytopenia.

INTRODUCTION

Standard of care for newly diagnosed glioblastoma includes surgery followed by radiotherapy and concomitant temozolomide and 6 maintenance temozolomide cycles[1].
Thrombocytopenia represents the main toxicity of this regimen: the frequency of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 (25,000-49,000/µl) and 4 (<25,000/ µl) thrombocytopenia in phase III clinical trials varied from 6% to 19.4%[2-6].
Consequences of thrombocytopenia include hemorrhage, with increased risk in patients treated with corticosteroids[7]. Moreover, thrombocytopenia necessitates dose reductions, delays of further courses, or discontinuation of chemotherapy which may compromise survival[8]. The only option to treat thrombocytopenia is platelet transfusions which ameliorates thrombocytopenia transiently and at high cost, but without allowing to continue chemotherapy. Romiplostim (AMG 531, Nplate®) is a thrombopoietin mimetic agent with a similar mechanism of action as thrombopoietin. The PLATUM study aimed at demonstrating that romiplostim allows adequate exposure to chemotherapy in glioblastoma patients experiencing temozolomide-induced thrombocytopenia.

METHODS

PLATUM was a phase II open label, multicenter single arm trial (Figure 1). The primary objective was to determine the proportion of newly diagnosed glioblastoma patients with CTCAE grade 3 thrombocytopenia induced by temozolomide up to the fifth maintenance temozolomide cycle who were able to receive 6 cycles when treated with romiplostim, providing class IV evidence for efficacy of romiplostim for the management of temozolomide-induced thrombocytopenia. Secondary endpoints included incidence of serious adverse events, number of postponed temozolomide cycles, duration of delays, number of patients

with recurrent CTCAE grade 3/4 thrombocytopenia, number of patients receiving platelet transfusions, and survival.

Inclusion criteria included histologically confirmed newly diagnosed glioblastoma, age≥18 years, ECOG performance status 0-2, intent to be treated with standard first-line concomitant and maintenance temozolomide chemotherapy with radiotherapy over a course of 6 weeks[2], and development of CTCAE grade 3/4 thrombocytopenia. Patients could be enrolled not earlier than one week after the end of radiotherapy to exclude potential interactions of romiplostim with radiotherapy. Further eligibility criteria included platelet counts > 100,000/µl, hemoglobin levels ≥9.5 g/dl, absolute neutrophil counts ≥1,000/µl, and absence of coagulopathy or hematological disease including thrombocytopenia before initiation of concomitant temozolomide.

Standard protocol approvals, registrations and patient consents

The study protocol and informed consent form were approved by the French ethics committee (CPP13/70). All participants provided written informed consent. The trial was registered on Clinicaltrials.gov (NCT02227576).

Sample size determination

The primary analysis was conducted to provide class IV evidence that romiplostim allows to administer 6 maintenance temozolomide cycles after an episode of grade 3/4 thrombocytopenia. According to Gerber and colleagues[9], 90% of patients who experience CTCAE grade 3/4 thrombocytopenia stop temozolomide chemotherapy before completing 6 cycles. PLATUM aimed at demonstrating that the percentage of patients treated with romiplostim and able to complete chemotherapy was significantly higher than 10% (p0=0.10; pA=0.35). Using type I error equal to 0.05 and 95% power, 31 evaluable patients had to be recruited. A Fleming's two-step design was chosen, with 20 subjects included in step 1 (a0=2; b0=6) and eleven subjects in step 2. An interim analysis was planned after recruitment of 20 evaluable patients in step 1. Three scenarios were pre-defined: (1) success

rate defined as patients receiving the six planned maintenance temozolomide cycles $\leq$ 2: termination for futility (p<P0), (2) success rate $\geq$ 6 patients: termination for success (p>P0), (3) success rate between 3 and 5 patients: enrollment of 11 more evaluable patients.

RESULTS

Patient characteristics

Twenty patients were enrolled in step 1 between July 2014 and December 2016. Concomitant temozolomide had been interrupted in 17 patients because of thrombocytopenia, but no dose reductions were reported. Ten patients presented with CTCAE grade 3/4 thrombocytopenia during concomitant temozolomide chemoradiotherapy (median 33 days; range 28-124) (Table 1). Enrolment could not start earlier than one week after completion of radiotherapy, accordingly, these 10 patients, plus six patients who developed grade 3/4 thrombocytopenia shortly after completion of radiotherapy, were enrolled prior to the start of maintenance temozolomide (period I). Four patients were enrolled thereafter (period II).

Romiplostim exposure

Romiplostim was administered weekly without interruption from enrollment to completion of temozolomide for a maximum of 6 cycles in 7 of 12 patients who completed 6 cycles of maintenance temozolomide. A median of 22 romiplostim injections was administered (range 1-45). The median cumulative dose of romiplostim was 14,000 µg (range 750-41,250 µg). The median dose per injection was 923 µg (range 446-984 µg). Three patients interrupted romiplostim, for a median delay of 29 days (range 14-36 days) due to platelet counts >400,000/µl. No interruption of romiplostim was observed for toxicity except for one patient who omitted one dose for pruritus.

Safety

Two patients went off study because of adverse events (Table 2). One patient presented with lower limb ischemia after 3 injections of romiplostim, however, ischemia had probably been preexisting. The other patient had renal insufficiency secondary to dehydration complicated by aspiration pneumonia not felt to be related to romiplostim.

Efficacy outcomes

Twelve of 20 patients received the 6 planned temozolomide maintenance cycles, corresponding to a success rate of 60% (95% confidence interval, CI, 36.05-80.88%). Accordingly, PLATUM was terminated for success. Of 16 patients enrolled in period I, 5 patients never started maintenance temozolomide: three for inefficacy of romiplostim and two for tumor progression; nine patients completed 6 cycles of temozolomide. Of 4 patients enrolled in period II, one never restarted temozolomide for an adverse event unrelated to romiplostim, the other 3 patients completed 6 cycles of maintenance temozolomide. Altogether, romiplostim was stopped for non-efficacy in 4 patients, and tumor progression and adverse events not related to romiplostim in two patients each. Recurrent CTCAE grade 3/4 thrombocytopenias were observed in 17 patients. A total of 33 platelet transfusions were administered, to a total of 9 patients (median of 2 transfusions per patient, range 1-12 transfusions).

Among the overall 12 patients who received 6 cycles of maintenance temozolomide, the median length of a temozolomide cycle while treated with romiplostim was 39 days (range 27-80). Temozolomide was postponed for a median of 8.5 days per cycle (range 0-52 days) after romiplostim initiation for these patients. Maintenance cycle delays were mainly related to thrombocytopenia (35 cycles). Other causes included neutropenia (2 cycles), thrombocytopenia plus neutropenia, thrombocytopenia plus general status alteration, and acute gastroenteritis (1 cycle each). A dose reduction of temozolomide was instituted in 10 patients.

At the time of the final analysis, 13 patients have experienced recurrence and 15 patients have died. PFS at 6 months was 85%. Actuarial median PFS after surgery was 14.4 months (95% CI 12.9-24.8 months). Actuarial median overall survival was 22.9 months (95% CI 10.0-28.7 months).

DISCUSSION

Relative to a historical benchmark[9], romiplostim allowed to increase the percentage of patients with temozolomide-induced grade 3/4 thrombocytopenia that were able to complete 6 cycles of maintenance temozolomide chemotherapy, from 10% to 60%. No severe adverse events attributed to romiplostim were reported. One pulmonary embolism was observed, not exceeding expectations, and no major bleeding was reported. There was no evidence for a detrimental effect of romiplostim for PFS or overall survival.

PLATUM was a small trial with inherent limitations. We cannot exclude that coexposure to drugs other than temozolomide, e.g., trimethoprim sulfamethoxazole or anti-epileptic drugs, contributed to thrombocytopenia. A randomized trial to confirm that romiplostim helps reducing platelet transfusions and bleeding complications, and, more importantly, improves outcome in patients presenting with chemotherapy-induced thrombocytopenia by allowing to complete chemotherapy is planned by the European Organization for Research and Treatment of Cancer. Such a trial should be conducted in a molecularly enriched chemosensitive patient population, e.g., those with MGMT promoter methylation who are most likely to benefit from prolonged exposure from chemotherapy.

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231 **TABLE**

232

233 **Table 1: Patient characteristics at baseline and during the concomitant and**
234 **maintenance treatment phases**
235

Baseline characteristics	
Gender, n patients (%) male female	 7 (35%) 13 (65%)
Age* median (min-max)	 60.5 years (33-72)
ECOG performance status, n patients (%) 0 1 2 3 Median	 3 (15%) 13 (65%) 3 (1(%) 1 (5%) 1 (range 0-3)
Type of surgery according to early postoperative MRI, n patients (%) biopsy partial resection subtotal resection** gross total resection	 7 (35%) 5 (25%) 2 (10%) 6 (30%)
IDH1^{R132H} mutation status, n patients (%) mutant wild type	 2 (10%) 18 (90%)
MGMT promoter methylation status, n patients (%) methylated non-methylated unknown	 5 (25%) 10 (50%) 5 (25%)
Pneumocystis jirovecii pneumonia prophylaxis at inclusion, n patients (%) atovaquone inhaled pentamidine	 2 (10%) 1 (5%)
Steroids within 14 days of registration, n patients (%)	16 (80%)
Anti-epileptic medication within 14 days of registration, n patients (%) levetiracetam levetiracetam + clozabam levetiracetam + perampanel pregabalin lamotrigine + clozabam none	 7 (35%) 1 (5%) 1 (5%) 1 (5%) 2 (10%) 8 (40%)
Median platelet count (/µl)(range) at first grade 3/4 thrombocytopenia	28,000 (6,000-48,000)

Time (median/range) from initiation of temozolomide chemoradiotherapy to first grade 3/4 thrombocytopenia	42 days (28-169)
Median lowest platelet count prior to registration (/µl)(range)	24,500 (6,000-59,000)*****
Median time from initiation of temozolomide chemoradiotherapy to lowest platelet count prior to registration	54.5 days (28-327)
Median platelet count at inclusion (/µl)(range)	53,500 (25,000-242,000)
Concomitant temozolomide and radiotherapy treatment phase	
Pneumocystis jirovecii pneumonia prophylaxis during radiotherapy, n patients (%) trimethoprim-sulfamethoxazole atovaquone inhaled pentamidine none unknown	 10 (50%) 2 (10%) 3 (15%) 3 (15%) 2 10%)
Dose of radiotherapy, n patients 58 Gy (in fractions of 2 Gy) 60 Gy (in fractions of 2 Gy) 62 Gy (in fractions of 2 Gy)	 1 18 1
Interruption of radiotherapy***, n patients	3
Median duration of concomitant temozolomide with radiotherapy	34 days (range 24-44)
Interruption of concomitant temozolomide with radiotherapy****, n patients	17
Grade 3/4 thrombocytopenia during temozolomide chemoradiotherapy, n patients yes no	 10 10
Time interval (median/range) between initiation of temozolomide chemoradiotherapy and grade 3/4 thrombocytopenia	33 days (28-124)
Maintenance temozolomide treatment phase	
Median time between end of radiotherapy and temozolomide initiation for 11 of 16 patients enrolled in period I that started maintenance temozolomide	58 days (range 27-180 days)
Median time between initiation of chemoradiotherapy and temozolomide initiation for 11 of 16 patients enrolled in period I that started maintenance temozolomide	102 days (range 78-222 days)
Grade 3/4 thrombocytopenia during maintenance temozolomide, n patients (%) yes no	 11 (55%) 9 (45%)
Time interval between initiation of maintenance temozolomide and grade 3/4 thrombocytopenia for 11 of 16 patients enrolled in period I that started maintenance temozolomide	40 days (16-282 days)

Median highest dose of temozolomide after romiplostim initiation among patients who completed 6 cycles of temozolomide	150 mg/m^2 (range 125-200 mg/m^2)
Median dose of temozolomide during maintenance treatment among patients who completed 6 cycles of temozolomide	150 mg/m^2 (115-187.5 mg/m^2)
Median dose of temozolomide used for the 6th temozolomide cycle among patients who completed 6 cycles of temozolomide	125 mg/m^2 (110-200 mg/m^2)
Outcomes with romiplostim	
Patients enrolled in period I (n=16) Started maintenance temozolomide Completed six cycles of temozolomide Stopped romiplostim for: - inefficacy - progressive disease - adverse event	 11 9 4 2 1
Patients enrolled in period II (n=4) Completed six cycles of temozolomide Stopped romiplostim for: - inefficacy - progressive disease - adverse event	 3 0 0 1

*A bone marrow biopsy was to be performed for patients aged 60 years or older in order to detect a potential fibrosis which would predict unresponsiveness to romiplostim. Ten of the 13 patients aged 60 years or more had a bone marrow biopsy which showed no bone marrow fibrosis in any patient.

**resection between 90 and 100%

***Radiotherapy was interrupted for 5, 10 and 44 days in 3 patients because of thrombocytopenia at 26,000/µl,16,800/µl (twice in one patient), and 6,000/µl and 30,000/µl, respectively

****Concomitant temozolomide was interrupted during radiotherapy in 17 patients, all for thrombocytopenia including 10 patients with grade 3/4 thrombocytopenia, for a median length of interruption of 10 days (range 2-61 days). The dose of temozolomide was not reduced during concomitant temozolomide with radiotherapy for patients without temozolomide interruption.

*****One patient was enrolled with a lowest platelet count of 59,000/µl (protocol violation). This patient was enrolled in period I and received 33 injections of romiplostim. Six cycles of temozolomide maintenance cycles were administered, 3 of which were delayed (median duration of delayed: 53 days).

Table 2: Summary of adverse events from the first administration of romiplostim up to 30 days after the last administration of romiplostim

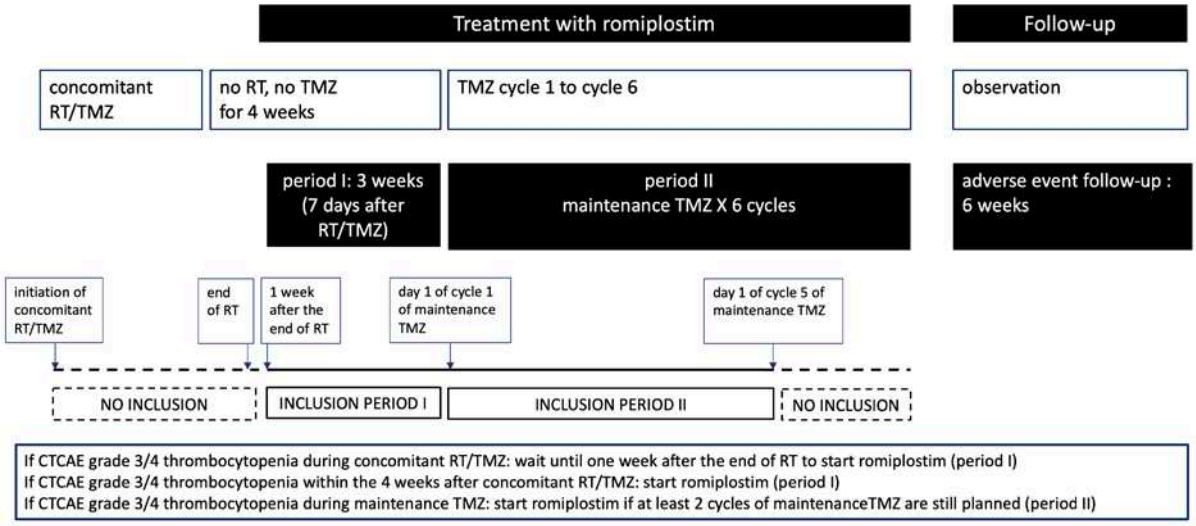
Events (number and %, all grades)	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3	CTCAE grade 4	CTCAE grade 5
Blood and lymphatic disorders: 33 (55%)					
Anemia: 10 (30%)	2 (not related) (10%)	5 (not related) (20%)	3 (not related) (15%)	0	0
Leukopenia: 4 (15%)	1 (not related) (5%)	2 (not related) (10%)	1 (not related) (5%)	0	0
Neutropenia: 6 (25%)	0	3 (not related) (15%)	2 (not related) (10%)	1 (not related) (5%)	0
Lymphopenia: 7 (20%)	0	4 (not related) (15%)	3 (not related) (10%)	0	0
Thrombocytopenia: 3 (15%)	NA	NA	1 (not related) (5%)	2 (not related) (10%)	0
Aplasia: 3 (15%)	0	1 (not related) (5%)	1 (not related) (5%)	1 (not related) (5%)	0
Vascular disorders: 7 (20%)					
Hematoma: 3 (15%)	0	3 (not related) (15%)	0	0	0
Arterial hypertension: 2 (10%)	2 (not related) (10%)	0	0	0	0
Lower limb ischemia: 1 (5%)	0	0	0	1 (not related) (5%)	0
Pulmonary embolism: 1 (5%)	0	0	1 (not related) (5%)	0	0
General disorders and administration site conditions: 32 (60%).					
Injection site hematoma: 2 (10%)	2 (related) (10%)	0	0	0	0
Fatigue: 26 (60%)	15 (12 not related; 3 related) (45%; 15%)	8 (7 not related; 1 related) (20%; 5%)	3 (not related) (15%)	0	0
Face edema: 1 (5%)	1 (not related) (5%)	0	0	0	0
General physical health deterioration: 2	0	0	1 (not related) (5%)	1 (not related) (5%)	0
(10%)	0	1 (not related) (5%)	0	0	0
Generalized edema: 1 (5%)	1 (not related) (5%)	0	1 (not related) (5%)	0	0
Falls: 2 (10%)					
Ear and labyrinth disorders: 2 (10%)					
Vertigo: 2 (10%)	2 (not related) (10%)	0	0	0	0
Infection and infestations: 10 (50%)					
Pneumopathy: 5 (25%)	0	2 (not related) (10%)	2 (not related) (10%)	0	1 (not related) (5%)
Gastroenteritis: 1 (5%)	1 (not related) (5%)	0	0	0	0
Urinary tract infection: 1 (5%)	1 (not related) (5%)	0	0	0	0
Oral fungal infection: 1 (5%)	0	1 (not related) (5%)	0	0	0
Sinusitis: 1 (5%)	0	1 (not related) (5%)	0	0	0
Cough: 1 (5%)	1 (not related) (5%)	0	0	0	0
Gastro-intestinal disorders: **30 (55%)**					
Nausea: 10 (25%)	6 (not related) (15%)	4 (not related) (20%)	0	0	0
Vomiting: 5 (20%)	2 (not related) (10%)	3 (not related) (10%)	0	0	0
Constipation: 6 (30%)	6 (not related) (30%)	0	0	0	0
Diarrhea: 3 (10%)	3 (not related) (10%)	0	0	0	0
Melena: 1 (5%)	0	1 (not related) (5%)	0	0	0
Abdominal pain: 3 (15%)	0	3 (1 not related; 2 related) (5%; 5%)	0	0	0
Increased gamma glutamyl transferase : 2	0	1 (not related) (5%)	1 (not related) (5%)	0	0
(5%)					
Metabolism and nutrition disorders: 7 (20%)					
Anorexia: 5 (10%)	3 (not related) (10%)	1 (not related) (5%)	1 (not related) (5%)	0	0
Vitamin D deficiency: 1 (5%)	0	1 (not related) (5%)	0	0	0

Polydipsia: 1 (5%)	0	1 (not related) (5%)	0	0	0
Renal and urinary disorders: 1 (5%)					
Acute renal failure: 1 (5%)	0	0	0	0	1 (not related)
Musculoskeletal and connective tissue disorders: 6 (30%)					
Arthralgia: 4 (20%)	3 (not related) (15%)	1 (not related) (5%)	0	0	0
Myopathy: 1 (5%)	0	0	1 (not related) (5%)	0	0
Myalgia: 1 (5%)	1 (related) (5%)	0	0	0	0
Nervous system disorders: 14 (50%)					
Intracranial hypertension: 3 (15%)	0	1 (not related) (5%)	0	1 (not related)* (5%)	1 (not related)* (5%)
Headache: 8 (30%)	2 (not related) (10%)	5 (not related) (20%)	1 (not related) (5%)	0	0
Seizure: 2 (10%)	0	1 (not related) (5%)	1 (not related) (5%)	0	0
Tremor: 1 (5%)	1 (not related) (5%)	0	0	0	0
Psychiatric disorders: 9 (40%)					
Anxiety: 4 (20%)	0	3 (not related) (15%)	1 (not related) (5%)	0	0
Depression: 2 (10%)	1 (not related) (5%)	1 (not related) (5%)	0	0	0
Insomnia: 2 (10%)	2 (not related) (10%)	0	0	0	0
Hallucinations: 1 (5%)	0	1 (not related) (5%)	0	0	0
Skin and subcutaneaous tissue disorders: 5 (20%)					
Dry skin: 1 (5%)	1 (not related) (5%)	0	0	0	0
Dermatitis allergicica: 1 (5%)	0	1 (not related) (5%)	0	0	0
Pruritus: 2 (5%)	0	2 (related) (5%)	0	0	0
Purpura: 1 (5%)	0	1 (not related) (5%)	0	0	0
Eye disorders: 1 (5%)					
Cataract: 1 (5%)	0	0	1 (not related) (5%)	0	0

Adverse events were classified by system organ class and graded according to CTCAE v4.0.
Hundred-seventy adverse events were documented in all patients (100%), 38 grade 3 to 5 adverse events were documented in 12 patients (60%), and 19 serious adverse events were documented in 11 patients

FIGURE

Figure 1. Design of the PLATUM trial[1]



***RT, radiotherapy; TMZ, temozolomide.**

[1] Patients were to receive weekly subcutaneous injections of romiplostim at a starting dose of 750 µg. Dose adjustments were based on weekly platelets counts. Four dose levels were defined: 250 µg, 500 µg, 750 µg and 1,000 µg. If platelet counts were higher than 400,000/µl, romiplostim was withheld and re-initiated at one dose level below when platelet counts dropped below 200,000/µl. In case of non-response, defined by platelet counts below 100,000/µl despite romiplostim injections, a maximum of 6 consecutive weekly injections were allowed. The administration of temozolomide was not permitted if platelet counts were below 100,000/µl. Patients were seen weekly for clinical and safety evaluation and administration of romiplostim. Brain MRI was performed every 3 months and tumor status was assessed using RANO criteria.

APPENDIX 1: Authors

Name	Location	Role	Contribution
Emilie Le Rhun, MD, PhD	University of Lille, France; CHU Lille, France; Oscar Lambret Center, Lille, France	Author	Design and conceptualized study; acquisition of data; analyzed the data; drafted the manuscript for intellectual content
Patrick Devos	University of Lille, France: CHU Lille, France	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Caroline Houillier, MD	APHP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France	Author	Interpreted the data; acquisition of data; revised the manuscript for intellectual content
Stéphanie Cartalat, MD	Hospices Civils de Lyon, France	Author	Interpreted the data; acquisition of data; revised the manuscript for intellectual content
Olivier Chinot, MD, PhD	Aix-Marseille University, France; AP-HM, CHU Timone, Marseille, France	Author	Interpreted the data; acquisition of data; revised the manuscript for intellectual content
Anna Luisa Di Stefano, MD	APHP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France	Author	Interpreted the data; acquisition of data; revised the manuscript for intellectual content
Clément Lepage	CHU Lille, France	Author	Major role in the acquisition of data; revised the manuscript for intellectual content

Nicolas Reyns, MD, PhD	University of Lille, France; CHU Lille, France	Author	Interpreted the data; revised the manuscript for intellectual content
François Dubois, MD	CHU Lille, France	Author	Interpreted the data; acquisition of data; revised the manuscript for intellectual content
Michael Weller MD	University Hospital and University of Zurich, Zurich, Switzerland	Author	analyzed the data; drafted the manuscript for intellectual content

REFERENCES

1. Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol. 2017;18:e315–e329.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987–996.
3. Gilbert MR, Sulman EP, Mehta MP. Bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370:2048–2049.
4. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370:709–722.
5. Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1100–1108.
6. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol. 2017;18:1373–1385.
7. Garcia Rodríguez LA, Hernández-Díaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. Arthritis Res. 2001;3:98–101.
8. Olawaiye AB, Java JJ, Krivak TC, et al. Does adjuvant chemotherapy dose modification have an impact on the outcome of patients diagnosed with advanced stage ovarian cancer? An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2018;151:18–23.
9. Gerber DE, Grossman SA, Zeltzman M, Parisi MA, Kleinberg L. The impact of thrombocytopenia from temozolomide and radiation in newly diagnosed adults with high-grade gliomas. Neuro-Oncol. 2007;9:47–52.